REMARKS

Amendments

Claims 1-30, 35-37 and 39 are canceled, claims 31-32, 34, 38, 42 and 43 have been amended, and claim 44 has been added. Upon entry of the amendment, claims 31-34, 38 and 40-44 will be pending. Support for the amended and added claims can be found in the specification, for example, on page 2, lines 26-27; page 5, lines 12-27; page 6, lines 1-10; page 8, lines 25-28, the Examples; the Figures; and in the claims as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. § 101

The Examiner has maintained the rejection of claims 31-34, and 38, and rejected new claims 40-43 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. The Examiner has found previous arguments unpersuasive.

Applicant respectfully traverses the rejection. Amended claim 1 is drawn to a transgenic mouse whose genome comprises a null chemokine receptor 9A allele. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> . . .

If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

. . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.

Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evident sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what

> is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> . . .
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken

advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached).

Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
>
> . . .
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> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**
>
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally

support the expression of that gene.

(p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an <u>invaluable tool for investigating gene function</u> on a genomic scale.

(p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. <u>This is a powerful method to investigate directly the importance and function of the gene</u>.

(p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

> Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.

(preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

> The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.

(p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

> Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.
>
> Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

In addition, commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, the presently claimed mouse has been ordered by and delivered to at least three large pharmaceutical companies. This acceptance more than satisfies the practical utility requirement

of section 101 as **it cannot be reasonably argued that a claimed invention which is actually being used by those skilled in the art has no "real world" use**. (see, for example, Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success); (Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand.")

If the Examiner requires an affidavit as evidence of such sales, the Applicant shall so provide one.

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

The Examiner provides a definition for "Specific Utility"- A utility that is specific to the subject matter claimed. ...' (page 3).

Applicant submits amended claim 31 is drawn to a transgenic mouse whose genome comprises a null chemokine receptor 9A allele; the specific polynucleotide for a chemokine receptor 9A allele is disclosed in Figure 1 as SEQ ID NO: 1. Further, claims 32 and 33 claim a statistically significant specific phenotype, or property, for the homozygous transgenic mouse of claim 42 (data shown in Table 1, page 56 of the instant specification; 1-p value vs. wild type controls = 0.99 (n = 10)). The Applicant thus submits that the claimed transgenic mouse is "specific" for the chemokine receptor gene of SEQ ID NO: 1; and the transgenic mouse of claim 42 has a "specific" observable property (rotarod phenotype).

The Examiner also provides a definition for "Substantial Utility"-" a utility that provides a real world use. ... An assay method for identifying compounds that themselves have a substantial utility define a "real world" context of use...".

Several specific uses for the claimed transgenic mouse appear in the instant specification that provides, for example, "...methods of identifying agents capable of affecting a phenotype of a transgenic animal." page 5, paragraph 4; and

"...a method of identifying agents having an effect on chemokine receptor 9A expression or function." page 5, paragraph 5.

Other such utilities for the present invention are provided throughout the specification, for example on page 20, paragraph 2 and page 33, paragraph 3, and in new claim 44.

Drug discovery and development is a substantial, real world utility. One skilled in the art understands how to use knockout mice in drug discovery.

For example, Shah states:

> Often knockouts are used for drug discovery and development in two ways, depending on whether the knockout results in a mouse that is defective in a specific function, or whether the knockout improves a particular condition or process. If the knockout replicates a disease phenotype, the knockout mouse can serve as an animal model for the disease. Such is the case for human diseases caused by single-gene loss-of-function mutations such as cystic fibrosis or muscular dystrophy. For example, cystic fibrosis is caused by a variety of mutations that individually result in nonfunctional ion transporters. A knockout in the mouse homolog for the gene that replicates the disease phenotype could serve as a mouse model of cystic fibrosis in which to test and develop treatments. But single-gene loss-of-function diseases are relatively rare.
> A more common use of mouse knockouts in drug discovery is in validating gene targets. More typically, a disease is due to an abundance of, rather than lack of, a gene product. In this case, knocking out the gene actually tells whether the gene would be a good drug target and lets researchers view what effect an antagonistic drug would have (Shah, Drug Discovery and Development, 2004, copy attached).

A retrospective study of knockout mouse phenotypes for the targets of the 100 best selling drugs in 2001 indicated that the targets modulate approximately 43 host protein targets. Of the 43 mammalian targets, 34 had been knocked out and 29 of the resulting phenotypes were informative as to gene function and pharmaceutical utility and, in most cases, provided a direct correlation between KO phenotype and the therapeutic effect of the drug (Zambrowicz et al., Nature Reviews/Drug Discovery, 2:38-51, page 40, second column, copy attached). Hence, "a retrospective evaluation of the knockout phenotypes correlate well with known drug efficacy; illuminating a productive path forward for discovering future drug targets. ... The data presented in this retrospective study of KOs of the top drug targets demonstrates the strong correlation that exists between phenotypes, mechanism of action and utility of associated therapeutics."

The Applicant submits that compound identification and target gene validation are two real world, well-established utilities for the transgenic mouse of the present invention.

The Examiner states the chemokine receptor 9A transgenic mouse of the present invention is not analogous to the gas chromatograph which is " a research tool with a well-defined function and highly specific use that does not necessitate further study of itself".

The Applicant submits the transgenic mouse is analogous to a gas chromatograph in several aspects. The chemokine receptor 9A transgenic mouse is a well-defined system: the transgenic phenotypes are compared directly to a wild-type mouse with the same genetic background. The transgenic mouse is also highly specific to the chemokine receptor 9A null allele. With any analytical instrument, the procedure is tailored to the analyte. An *in vivo* system, such as a transgenic mouse, is designed to test compounds and environmental conditions which affect expression or function of the gene product. The transgenic mouse is a tool to test the functions of a gene; much as the gas chromatograph is a tool to test the presence of a single compound.

The Examiner quotes utility guidelines that "further research is not a substantial utility". The Applicant believes the transgenic mouse of the present invention does not require further study of itself to be useful to test agents or compounds which affect the claimed phenotype. The instant specification provides specific methods for providing the transgenic mouse, for example on page 48, Example 1. Further, the rotarod method of testing is described on pages 25, 55 and 56. The rotarod test is a well known neurological test in the scientific literature (Baik et al., Nature 377:424-428(1995); Boyce et al., Exp. Neurol., 155: 49-58 (1999); Liu et al, PNAS-USA 94:8138-43 (1997); Rozas et al., J. Neurosci. Meth. 83:165-175 (1998)). More than one neurological condition may affect performance in the rotarod test; just as more than one compound may have the same retention time in the gas chromatograph. The present invention further provides a method of identifying agents having an effect on chemokine receptor 9A expression or function on page 5 of the instant specification.

The Examiner states that the "instant invention does not have utility because the mice exhibit a phenotype that fails to be correlated to the function of the chemokine 9A receptor. There is no correlation between the observed phenotypes and the knockout of the chemokine 9A receptor gene: thus the utility of the mice is not readily apparent."

The Applicant respectfully disagrees. As stated above, the data shown in Table 1, page 56 of the instant specification is statistically significant. The 1-p value vs. wild type controls = 0.99 for rotarod trial 3 fall speed (n = 10). Since the only difference between homozygous and wild-type mice is the null mutation of the chemokine 9A receptor gene, the phenotype is correlated to the chemokine 9A receptor knockout mouse.

The Examiner states "it is clear from all of the art provided by Applicants that knockout mice are used to elucidate gene function, which is not considered a substantial utility."

The Applicant respectfully disagrees; at least thirteen U.S. patents have been issued which describe methods for gene function determination or manipulation (see, for example, 6,733,969 "Expression monitoring for gene function identification"; 6,673,567 "Methods of determination of gene function"; 6,410,257 "Methods to assay gene function with viral vectors"; and 5,750,825 "Mouse with defective endotheline-1 gene function").

The Examiner states "neither specification nor the art of record provides evidence of the existence of a correlation between decreased agility, coordination or balance and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse encompassed by the claims".

The Applicant disagrees. In addition to the statistically significant correlation disclosed in the specification on pages 50 and 51, the art at the time of filing found that chemokines regulate hippocampal neuronal signaling and gp120 toxicity (Meucci et al., Proc. Natl. Acad. Sci. USA 95:14500-14505 (1998)). Meucci et al. found that hippocampal neurons contain several types of chemokine receptors by RT-PCR, including CCR9. Further support is found in instant specfication which states

> Chemokines are chemotactic cytokines released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation. The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, *Trends Pharm. Sci.* 15:159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal through the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. (page 1, lines 25-26). ...(HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome, AIDS) and degeneration of the central and peripheral nervous system (page 2, lines 28-31).

Several papers published since the time of filing have implicated the chemokine 9A receptor(CCR9) in multiple disease states. Youn et al. showed that activation of the CC chemokine 9 receptor (CCR9), a thymus-specific chemokine receptor, led to potent cFLIP(L)-independent resistance to cycloheximide-induced apoptosis and modest resistance to Fas-mediated apoptosis and suggested signaling components involved in the CCR9-mediated

antiapoptosis could be a framework for cell survival mechanisms and may provide options for therapeutic interventions for neurodegenerative diseases or T cell malfunctioning (Youn et al., Apoptosis 7:271-276 (2002). Other disease states mediated by CCR9 include acute and chronic lymphocytic leukemia, metastasis of the small intestine, small bowel Crohn's disease, and prostate cancer cell migration and invasion. Qiuping et al. suggested differential functions of CCR9/CCL25 in distinct types of cells. CD4 and CD8 double-positive thymocytes used CCR9/CCL25 for migration, homing, development, maturation, selection, cell homeostasis, whereas malignant cells, particularly T-ALL CD4(+) T cells, used CCR9/CCL25 for infiltration, resistance to apoptosis, and inappropriate proliferation. (Qiuping et al., CC chemokine ligand 25 enhances resistance to apoptosis in CD4+ T cells from patients with T-cell lineage acute and chronic lymphocytic leukemia by means of livin activation, Cancer Res. 64:7579-87 (2004)). Functional CCR9 expression is associated with small intestinal metastasis (Letsch et al., J. Invest. Dermatol. 122:685-90 (2004). Singh et al. showed neutralization of CCL25-CCR9 interactions impaired the migration and invasion potential of the LNCaP and PC3 prostate cancer cell lines and suggested that the expression and activation of CCR9 affect cancer cell migration, invasion, and MMP expression, which together may affect prostate cancer metastasis (Singh et al., Clin. Cancer Res. 10:8743-50 (2004)). Clearly, the chemokine receptor 9A transgenic mouse has specific and substantial utility.

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the chemokine 9A receptor gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying chemokine 9A receptor gene function and may be used for identification of agents affecting rotarod performance and motor coordination, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art. Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 31-34, 38, and 40-43 because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of

either a specific or substantial asserted utility or a well-established utility as set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, it is Applicant's position that the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention.

The Examiner states that it would have required undue experimentation to make/or use the invention as claimed.

The Applicant respectfully disagrees. Both the method of providing the transgenic mouse, and the method of using the mouse in rotarod testing to identify agents capable of modifying the effect of a null allele are clearly disclosed in the present invention, as described above.

The Examiner argues that behavioral test results are strain dependent and subject to the "hitchhiking effect" and the Examiner suggests either testing a large number of mice or many backcrosses to over come this potential effect.

In all behavioral tests, the mice were compared with age- and gender- matched wild-type control mice of the same generational backgrounds, generally F2N1 mice. Thus, the claimed mice were compared with control mice having identical backgrounds.

With regard to background effect, the mice used in Applicant's experiments were of uniform background. As clearly stated in the claims, the observed phenotypes are relative to wild-type control mice. Comparison was made with age, gender and strain-matched control mice. Thus, the backgrounds of the control mice and the claimed transgenic mice are identical.

Applicant points out that the analyses set forth in the specification are not based on a single mouse. Rather, as is standard in the art (see Crawley), all behavioral tests set forth in the Examples were performed using at least ten (10) homozygous mice and compared with at least ten (10) wild-type control mice (numbers not shown). The data underlying the results, including the number of mice, are set forth in Deltagen's commercial database product, DeltaBase, which is licensed to Merck, Pfizer and GlaxoSmithKline, among others. If the Examiner requires an affidavit to this effect, the Applicant shall so provide one.

Applicant additionally points out that all of the employees and consultants involved in Deltagen's pathology group are either MD's or DVM's, and many in addition hold PhD degrees. At least sixteen (16) of the employees or consultants are board certified ACVP or ABP. Unless the Examiner has reason to doubt the credibility of the reported results, the burden remains on

the Examiner to set forth a *prima facie* case. Unless and until the Examiner is able to do so, the Applicant respectfully requests withdrawal of the rejections.

The Examiner argues that the phenotype "may be" a result of a background marker gene.

With regard to such so called "hitchhiker genes," according to Wolfer *et al.*,: "..the possibility exists that an apparent effect of a null mutation could be due to a flanking 129 gene. Generally, the problem is disregarded because it imposes control strategies deemed costly, and because the statistically expected number of confounding flanking genes is relatively low" (emphasis added) (2002, *TRENDS in Neuroscience*, 25:336-340; page 336).

"Hitchhiker alleles" are also not relevant in this situation because the results are not based on a single mouse. All of the experiments were performed on cohorts of mice, KOs and wildtype controls. Thus, an outlier due to some combination of alleles and the KO gene would not be reported as a significant phenotype.

The Examiner states the specification fails to enable disrupting any chemokine receptor 9A gene in a mouse; the specification teaches only one chemokine receptor 9A sequence (SEQ ID NO: 1).

The Applicant submits the present invention also provides a targeting construct and methods of producing the targeting construct that when introduced into stem cells produces a homologous recombinant. In one embodiment, the targeting construct of the present invention comprises first and second polynucleotide sequences that are homologous to the chemokine receptor 9A gene. Other chemokine receptor 9A gene sequences may be easily found, for instance, in the NCBI data base and applied to the disclosed techniques without undue amount of added experimentation.

The Examiner states claim 34 is to a cell from a mouse comprising a disruption of the chemokine receptor 9A gene, and that such cell will not exhibit a phenotype of the mouse from which the cell is isolated.

The Applicant agrees that a cell from the transgenic mouse will not exhibit a phenotype of the mouse from which the cell is isolated. However, several uses for the claimed cell are provided throughout the specification and may be found, for example, on page 18, lines 27-31; page 19, lines 21-26; page 33, paragraphs 2-4, page 34, paragraph 1, page 42, paragraphs 2-3 and page 43, paragraphs 1-3.

The Examiner expressed concern that claim 38 was not enabled, because it did not specify that a mouse embryonic stem cell should be implanted into the uterus of a pseudopregnant mouse. Claim 38 has been amended to address Examiner's concern.

The Examiner rejects claims as allegedly failing to comply with the written description requirement. The Examiner argues that the specification fails to describe what other sequences, other than SEQ ID NO:1, falls into the genus of chemokine receptor 9A genes.

The written description is evaluated with respect to the claimed invention. In this case, what is claimed is a transgenic mouse with a null chemokine receptor 9A allele. As set forth above, the preferred methods utilize PCR amplification using primers which are developed based on knowledge of any portion of the chemokine receptor 9A allele, whether that allele is derived from a mouse or any other homologous chemokine receptor 9A sequence from another species. The primers can be developed based on EST sequences, genomic or cDNA sequences. In fact, knowledge of the sequence of the mouse chemokine receptor 9A gene is not even required to make the knockout mouse.

The Examiner cites *Fiers v Revel* and *Amgen v Chugai* for the proposition that the nucleic acid itself is required.

Both cases are clearly distinguishable from the present case. Both involved patents which claimed DNA sequences encoding certain proteins. Both cases involved the issue of when the applicant was in possession of the claimed nucleotide sequence.

In the present case, Applicant is not claiming a DNA sequence. Moreover, the mouse chemokine receptor 9A gene sequence is disclosed in the specification. Applicant submits that neither case cited by the Examiner is relevant to the present situation.

The Examiner cites *Fiddes v Baird* for the proposition that claims directed to mammalian FGF's were found to be unpatentable due to lack of written description.

Fiddes is likewise clearly distinguishable. In *Fiddes*, applicant Baird was claiming mammalian FGF although their specification disclosed a single species, a bovine pituitary FGF. Baird was not even in possession of the natural gene encoding bovine pituitary FGF.

In the present case, Applicant is not claiming mammalian chemokine receptor 9A, nor is Applicant even claiming mouse chemokine receptor 9A. Applicant is claiming a mouse having a null mouse chemokine receptor 9A allele, a single species. Applicant submits that one skilled in the art would acknowledge that Applicant was in possession of the claimed invention.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner also states that claim 34 is vague as to the metes and bounds of the claims. Claim 34 has been amended to address Examiner's concern.

Examiner also stated that claim 38 "states that a pseudopregnant mouse "gives birth". Claim 38 has been amended to address Examiner's concern. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 31, 34, 38, 40 and 41 as being unpatentable over Cappechi in light of Zaballos. Capecchi is cited as teaching general methods of creating knockout mice. Zaballos is cited as disclosing the sequence of the mouse CCR9 gene. The Examiner argues that it would have been obvious to make the claimed invention modify the knockout technology of Capecchi by use of a targeting vector for the disruption of the known chemokine receptor 9A.

As a preliminary matter, Applicant questions how the Examiner can argue that the requisite motivation exists to create the claimed invention, when the Examiner argues above that the claimed invention has no patentable utility and that one skilled in the art would not know how to use the invention.

A proper analysis under section 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and (2) whether the prior art would also have revealed that in so making, those of ordinary skill would have a reasonable expectation of success (*In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

Neither factor is satisfied here. The cited references, neither alone or in combination, teach or suggest the presently claimed invention. The claims as amended are drawn to a transgenic mouse whose genome comprises a null chemokine receptor 9A allele. The Examiner has not cited any evidence in the references that this gene be disrupted.

Moreover, one of ordinary skill would not have a reasonable expectation of success in making the claimed invention. Zaballos discloses mouse chemokine receptor 9A cDNA. Capecchi requires knowledge of the genomic sequence and restriction mapping to create a

targeting vector (Applicant questions whether Capecchi provides an enabling disclosure with regard to the making of any targeting vector or knockout mouse). Such information is not disclosed in either reference. Therefore, one of skill would have no reasonable expectation of arriving at the claimed invention. Therefore, the claimed invention would not have been obvious to one of skill in the art. Withdrawal is respectfully requested. In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

5-9-05

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